Flavell *et al.* (*Cancer Research*, 57:4824-4829, 1997). This rejection is respectfully traversed.

Mehta *et al.* teaches that retinoid-stimulated upregulation of CD38 antigen expression enhances the effectiveness of an anti-CD38-immunotoxin against cultured leukemia cells. Assuming *arguendo* that **Mehta** *et al.* suggests that approach may have clinical utility in the treatment of certain leukemias, **Mehta** *et al.* nevertheless contains no specific teachings regarding how this may be accomplished.

The Examiner argues that **Flavell** *et al.* teaches a method of treating a mouse carrying a human B-cell lymphoma through administration of an anti-CD38-saporin immunotoxin at a dosage falling within the range claimed by the instant invention. The Examiner's arguments notwithstanding, **Flavell** *et al.* in fact shows that the administration of a single anti-CD38-saporin was relatively ineffective in treating the animals. Only 10% of the animals treated with anti-CD38-saporin alone survived for the entire 300 day course of the experiment. Effective treatment was only obtained when the mice treated with a triple combination cocktail of anti-CD19, anti-CD22, and anti-CD38-saporin immunotoxins. In

contrast to the instant invention, **Flavell** *et al.* does not teach any methods of enhancing the expression of a target molecule on the surface of a tumor cell. Instead, **Flavell** *et al.* teaches that targeting multiple cellular markers enables the immunotoxins to reach cells which fail to express one or more of the target molecules and enables the delivery of additional toxin to multiple-target expressing cells via delivery of toxin by more than one conjugate. Furthermore, the teachings of **Flavell** *et al.* lean toward even more complicated cocktails of multiple immunotoxins rather than any method of enhancing the effectiveness of a single immunotoxin.

One of skill in the art would not have been motivated to combine the teachings of **Mehta** *et al.* and **Flavell** *et al.* as these references teach away from each other. **Mehta** *et al.* focuses on improving the effectiveness of single immunotoxin while **Flavell** *et al.* teaches that combinations of multiple immunotoxins are necessary for effective treatment. Nevertheless, even if the combination was contemplated by one of skill in the art, it would not have been obvious whether the retinoid-induced enhancement of CD38 expression would be sufficient to overcome the failure of treatment with anti-CD38 immunotoxin alone to cure the majority

of the mice. To establish this fact would require extensive experimentation such as that in the instant specification to demonstrate that the retinoid enhancement of CD38 expression was effective enough to enable a single anti-CD38 immunotoxin to kill all of the leukemia cells in a sample. Therefore, the Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 1-3 and 7-11 over **Mehta** *et al.* in view of **Flavell** *et al.* be withdrawn.

Claims 1, 5-9 and 11 stand rejected under 35 U.S.C. §103(a) as unpatentable over **Mehta** *et al.* (Proceeding of the American Association for Cancer Research, 38:88, 1997) in view of **Flavell** *et al.* (Cancer Research, 57:4824-4829, 1997), in further view of **Mehta** *et al.* (Proceeding of the American Association for Cancer Research, 35:92, 1994). This rejection is respectfully traversed.

As argued above, **Mehta** *et al.* (1997) and **Flavell** *et al.* use methods for the treatment of lymphoma and leukemia that are sufficiently different so that the combination thereof would not have been obvious. **Flavell** *et al.* contains no teachings on methods to enhance the expression of a cellular target and required a combination of three separate immunotoxins, each against a

different cellular target, to cure all of the mice implanted with human lymphoma cells. Anti-CD38 immunotoxin treatment alone was ineffective in curing the mice of the implanted lymphoma cell lines, resulting in a 90% mortality rate over the course of the experiment. **Mehta** *et al.* (1994) merely reports that retinoic acid enhances expression of myeloid leukemia cells. Therefore, while **Mehta** *et al.* (1994) may teach all trans-retinoic acid dosages in the range of the instant invention, **Mehta** *et al.* (1994) provides no additional teachings on the use of retinoic acid to enhance the effectiveness of immunotoxin treatment. Therefore, the addition of **Mehta** *et al.* (1994) to the combination of **Mehta** *et al.* (1997) and **Flavell** *et al.* still provides no evidence that the combination of retinoid pre-treatment with a single component anti-CD38 immunotoxin will destroy enough of the targeted tumor cells to be effective as a leukemia and lymphoma treatment. Therefore, the Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 1-3 and 7-11 over **Mehta** *et al.* (1997) in view of **Flavell** *et al.* in further view of **Mehta** *et al.* (1994) be withdrawn.

This is intended to be a complete response to the Office Action mailed December 7, 2000. Applicants submit that the

pending claims are in condition for allowance. If any issues remain, please telephone the attorney of record for immediate resolution.

Respectfully submitted,

DATE: Feb 28, 2001

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